CONCISE REPORT

# Practical progress in realisation of early diagnosis and treatment of patients with suspected rheumatoid arthritis: results from two matched questionnaires within three years

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**Background:** Early diagnosis and treatment with disease modifying antirheumatic drugs (DMARDs) have been advocated for patients with rheumatoid arthritis (RA). This survey focuses on the individual definitions and treatment modalities of rheumatologists, and aims at determining the practical realisation of these concepts.

**Methods:** A questionnaire to be self completed was handed out at the EULAR Symposium 1997. The main issues dealt with were definition, referral time, diagnosis, follow up, and treatment of early RA. Of the 111 participants, who were from all continents and all age groups, 85 (77%) gave their name and address. In 2000, the same questionnaire was sent to these 85 primary respondents. Forty four questionnaires (52%) were returned, and their results were matched and further evaluated.

**Results:** The definition of early RA was heterogeneous, but two of three rheumatologists use the term "early" for symptoms shorter than three months. There was a drift towards acceptance of involvement of fewer affected joints. Serological tests obtained for early diagnosis were mostly rheumatoid factor and antinuclear antibodies, usually in combination (approximately 70%), while other tests (antikeratin antibodies, antiperinuclear factor, anti-RA33) were used rarely, but increasingly (21–25% all together). No significant change in the lag time of referral to the specialist of patients with suspected early RA was seen within these three years (<3 months for 50%, >6 months for 20%), while the proportion followed up during the first three months increased. At both times, every second rheumatologist started DMARD treatment only when the 1987 American College of Rheumatology (ACR) criteria were fulfilled. However, in 1997 about 10% were willing to wait for erosions before starting DMARDs, while none did so in 2000. Methotrexate, sulfasalazine, and antimalarial drugs were the most commonly prescribed DMARDs in early RA, with the first two of these still being in increasing use.

**Conclusion:** The understanding of "early" rheumatoid arthritis is heterogeneous, but the vast majority of the rheumatologists surveyed regard symptom duration of <3 months as early. Rheumatoid factor was the most useful laboratory support in early diagnosis. Because there has been no shortening of referral time of patients with new RA within the past three years, and many rheumatologists start DMARDs only when the ACR criteria are fulfilled, it is concluded that guidelines for early referral, as well as for early (rheumatoid) arthritis, are needed.

Over many decades disease modifying antirheumatic drugs (DMARDs) have been used reluctantly in rheumatoid arthritis (RA), while at the same time symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has been advocated at early stages of the disease, and remission was thought to be quite common.[1 2] It has been shown that this "therapeutic pyramid" is insufficient to prevent joint damage[3] and the early use of DMARDs has been propagated during the past decade.[4 5] In fact, several trials have shown the efficacy of the traditional DMARDs in early arthritis,[6–10] but "early arthritis" is ill-defined: in some studies a disease duration of up to three years was accepted,[6 7] whereas other protocols required a much shorter maximum duration of symptoms.[8–10]

In this study we analysed the results of a survey performed among rheumatologists. Important aspects were to explore what rheumatologists describe as "early" RA, and to determine the average lag time of referral to the specialist for patients with suspected RA and to initiation of DMARD treatment.

## METHODS

A questionnaire to be self completed concerning early RA was designed. The questions focused on definition, referral time of patients, diagnostic approach, follow up of these patients, and treatment of patients with early RA (table 1). The questions were of closed style type, mostly offering categories of different answers. The first questionnaire was handed to participants at the EULAR Symposium in November 1997. One hundred and eleven questionnaires were returned. Of these respondents, 94 (85%) were rheumatologists, nine (8%) rheumatologists in training, six (5%) non-rheumatological clinicians, and two (2%) basic scientists. Fifty three (48%) were working in Europe, 58 (52%) in countries outside Europe, and all continents were represented. The respondents' affiliations were universities for 59 (53%), city hospitals for 43 (39%), and private practices for nine (8%).

Eighty five (77%) of the primary respondents also gave their name and postal address. In August 2000, these 85 colleagues were sent a follow up questionnaire which was identical to the first one; 44 (52%) responded. As before, the responders were primarily rheumatologists (42/44 (95%)), and their affiliations were similar to those previously (25 (57%) at universities, 15 (34%) at city hospitals, and four (9%) in private practices).

**Abbreviations:** ACR, American College of Rheumatology; AKA, antikeratin antibodies; APF, antiperinuclear factor; DMARDs, disease modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SSZ, sulfasalazine

**Table 1** Items included in the questionnaire

| Topic | Item(s) | Possible answers |
|---|---|---|
| Definition | What do you regard as early RA?<br>A. Type of arthritis (at least)<br>B. Duration of symptoms (one answer) | A. At least: polyarthritis (>5 joints)/oligoarthritis (2–5 joints)/monarthritis<br>B. <6 Weeks/<3 months/<6 months/<12 months/other, please specify |
| Referral time | How long on average does it take from onset of their symptoms until patients with arthritis are referred to you? (one answer) | <6 Weeks/<3 months/<6 months/<12 months/>12 months |
| Diagnostic approach | Which serological tests do you use in early diagnosis? (several answers) | Rheumatoid factor/antinuclear antibodies/antikeratin antibodies/antiperinuclear factor/anti-RA33 |
| Follow up of patients | How often do you see your patients with early arthritis during the first 3 months? (one answer)<br>How many patients with early arthritis do you see each year? | Every 2 weeks/every month/every 3 months/not at all |
| Treatment | When do you start DMARD treatment in patients with newly diagnosed RA? (one answer)<br><br>In newly diagnosed patients, which DMARDs do you prescribe most commonly? (maximum of two answers) | When erosions have occurred/when ACR criteria are fulfilled/when RA is suspected/when NSAIDs have failed <12 months/>6 months/>3 months/other, please specify<br>Azathioprine/chloroquine/hydroxychloroquine/chlorambucil/cyclophosphamide/cyclosporin A/D-penicillamine/gold compounds oral/gold compounds parenteral/methotrexate/sulfasalazine/other, please specify |

Data were registered and processed using version 10.0 of the Statistical Package for the Social Sciences. The questionnaires returned in 2000 were matched individually with those from 1997. Also, we present graphically the results of all 111 primary respondents to provide an estimate of potential non-responder bias.

## RESULTS

### Definition of early RA

Firstly, the participants were asked to define early arthritis by type of arthritis and duration of symptoms (table 1). Whereas in 1997 9% regarded monarthritis as a potential manifestation of early RA, in 2000 18% did so, while the proportion requiring

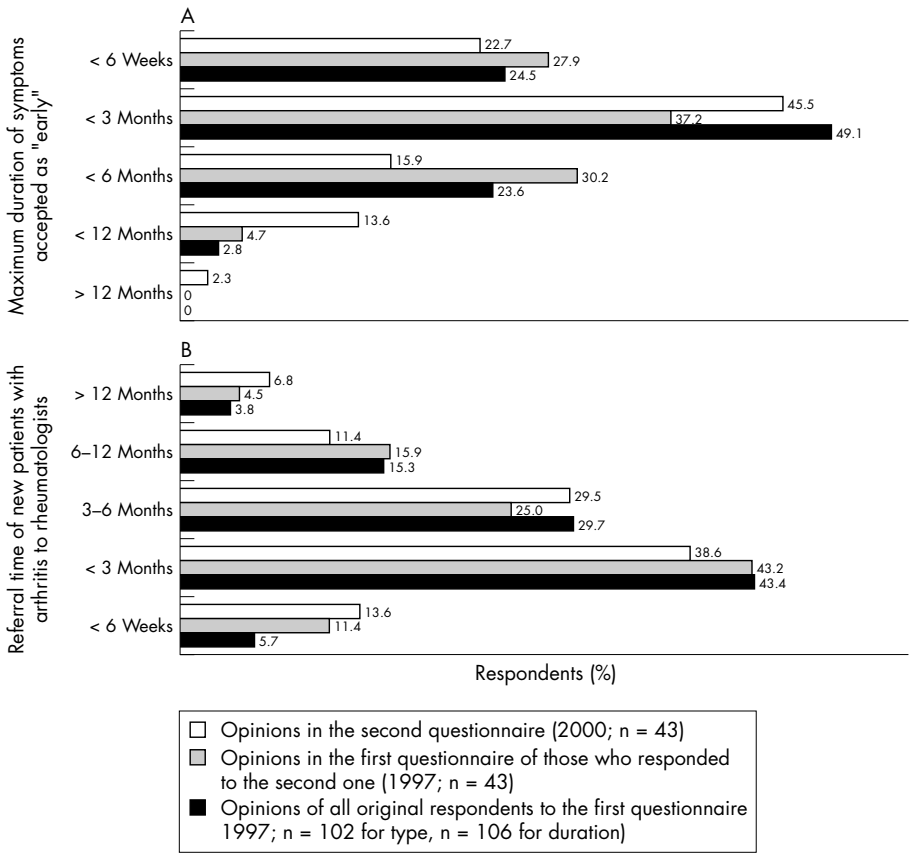


**Figure 1** (A) What maximum duration of symptoms do you still regard as early RA? (Only one answer was possible): bars represent the percentage of valid answers. (B) How long on average does it take from onset of their symptoms until patients with arthritis are referred to you? (Only one answer was possible): Bars represent the percentage of valid answers.

the presence of polyarthritis decreased by 20% (28% in 1997 to 23% in 2000). At both times approximately two of three rheumatologists would use the term "early RA" only if the duration of symptoms was <3 months (fig 1A).

The numbers of so-defined patients with early arthritis seen each year by the rheumatologists were similar at both times: the median number (and quartiles) of patients with early RA seen each year was 20 (10; 35) in 1997 and 18 (10; 50) in 2000. The median proportion of patients with early RA among all patients with RA seen each year was 11.3% (5.8%; 22.1%) in 1997 and 13.7% (6.3%; 20.0%) in 2000.

### Referral time of patients with suspected RA to rheumatologists (fig 1B)

Early referral of patients with symptoms of arthritis or suspected RA is mandatory for early diagnosis and treatment. During the past three years no significant change took place. Almost 50% of the respondents indicated that patients with arthritis were referred >3 months from onset of disease, while 54.6% (1997) and 52.2% (2000) stated a referral time of <3 months.

### Serological tests in early diagnosis

Apart from clinical presentation, we asked about the serological tests that were used to support diagnosis of early RA. Traditional tests that have been shown to be useful in diagnosis of RA were offered[11]: rheumatoid factor (RF), antikeratin antibodies (AKA), antiperinuclear factor (APF), and anti-RA33. RF testing was used by all respondents, but only a small proportion used the other serological tests (AKA, APF, anti-RA33) to support a diagnosis of early RA (18% in 1997, 25% in 2000). Also, antinuclear antibodies were used by 70% for differential diagnostic purposes.

### Follow up of patients with early RA

Most rheumatologists prefer monthly follow up visits for their patients with early arthritis during the first three months (66% in 1997, 52% in 2000). There was a notable shift towards more frequent (two weekly) follow up (16% in 1997, 26% in 2000), but the proportion of rheumatologists who were seeing their patients less often (once or not at all during the first three months) was similar at both times (18% *v* 21%).

### Treatment of early RA

At both times almost every second participant (49%) would start treatment with DMARDs when American College of Rheumatology (ACR) criteria for RA were fulfilled (fig 2A). Importantly, whereas in 1997 almost 10% were waiting for evidence of erosions before initiating DMARD treatment, in 2000 none did so. The proportion of respondents who would start DMARDs if suspecting RA even in the absence of four ACR criteria increased by one third (27.9% to 37.2%).

DMARD types employed in patients with newly diagnosed RA were mostly methotrexate (MTX), sulfasalazine (SSZ), and antimalarial drugs (fig 2B), with the first two still increasing (89% and 64% in 2000, which is a relative increase of 8% and 17%, respectively, during the past three years), and the latter in relatively unchanged proportion. Also, cyclosporin A was occasionally used as the first DMARD, while cyclophosphamide, chlorambucil, and auranofin (oral gold) were not used at all in patients with new RA in 2000 by the participating rheumatologists. The use of parenteral gold compounds decreased by 40% in the daily practice of the respondents. The participants were asked to select their two favourite DMARDs in this question: those who were using MTX, most commonly also liked to prescribe SSZ and vice versa, while those using antimalarial drugs mostly preferred MTX as alternative option (data not shown).

## DISCUSSION

About 10% of patients with RA seen by the participating rheumatologists had "early" RA. The interpretation of this proportion is problematic, as we found a considerable heterogeneity in what rheumatologists define as "early". Contrary to a recent report,[12] the present data suggest that in the opinion of international rheumatologists there is still a considerable lag period of patient referral: about half of the rheumatologists see their patients for the first time beyond the three months margin which most of them regard as the borderline of "early disease". Improved referral is needed.[13]

Support for diagnosis of RA comes from laboratory tests, mainly for RF. A significantly raised RF indicates those with increased susceptibility to developing RA,[11–14] and thus, is sensitive in the early diagnosis of patients with suspected symptoms of RA.[15] Newer markers of RA (AKA, APF, anti-RA33) were only used by a small proportion of the respondents, but have been increasingly used in the past three years.

One limitation of analysing questionnaires is bias. In this study three main sources of bias are possible. Firstly, a selection was made by choosing attendants of an international rheumatology meeting. Secondly, respondents to the first questionnaire might not have been a random sample of the attendants at the meeting, but rather participants who were more interested in RA, early RA, or treatment of RA. Bias on these two grounds can be regarded as directed towards the selection of opinion leaders, and thus, a real random sample might have shown an even smaller transposition of early diagnosis and treatment into clinical practice. Finally, the response rate to the second questionnaire in 2000 was 52%, raising the issue of non-response bias. One source of non-response might be the personalisation of the questionnaires, but this seems unlikely as all non-responders in 2000 participated voluntarily in 1997 and had voluntarily given their names. To provide a method to estimate the effect size caused by this type of bias, data on the opinions of the original participants are also presented in the figures. Despite these sources of potential bias, the value of this study lies in the broad representation of the respondents, who were from 35 countries and all continents.

At both the time points 1997 and 2000 the most commonly used DMARDs were MTX, SSZ, and antimalarial drugs. Interestingly, although there were two major differences between the responses for most other questions, the treatment behaviour appeared to have changed: gold salts were used 45% less frequently in 2000 than in 1997, while the use of SSZ and MTX was still increasing. The use of antimalarial drugs remained relatively stable. It will be interesting to learn of changes of treatment behaviour with the introduction of the newly approved DMARDs.

The most important aspect of this study is the opinion of the practising rheumatologists that RA should be regarded as early only within the first three months from onset of symptoms. This is in line with conclusions from clinical and from observational studies of early RA,[16 17] but has been derived by simple questioning of practising rheumatologists. The congruence of data obtained from prospective studies and results from questionnaires gives this time frame additional validity. Secondly, we found that almost 50% of rheumatologists await fulfilment of classification criteria of disease (the 1987 ACR criteria) before starting treatment with DMARDs. However, these criteria are not useful in early diagnosis,[18] but it may be understandable that, given the lack of diagnostic criteria for early RA, for many rheumatologists the initiation of potentially toxic drugs is not justified before a diagnosis is unequivocally established. Therefore, to better define early arthritis a core set and revised recommendations are needed. This demand for definitions is not only an academic need (for example, in clinical trials), but is also important in daily practice, where one major decision is when to start DMARDs. With

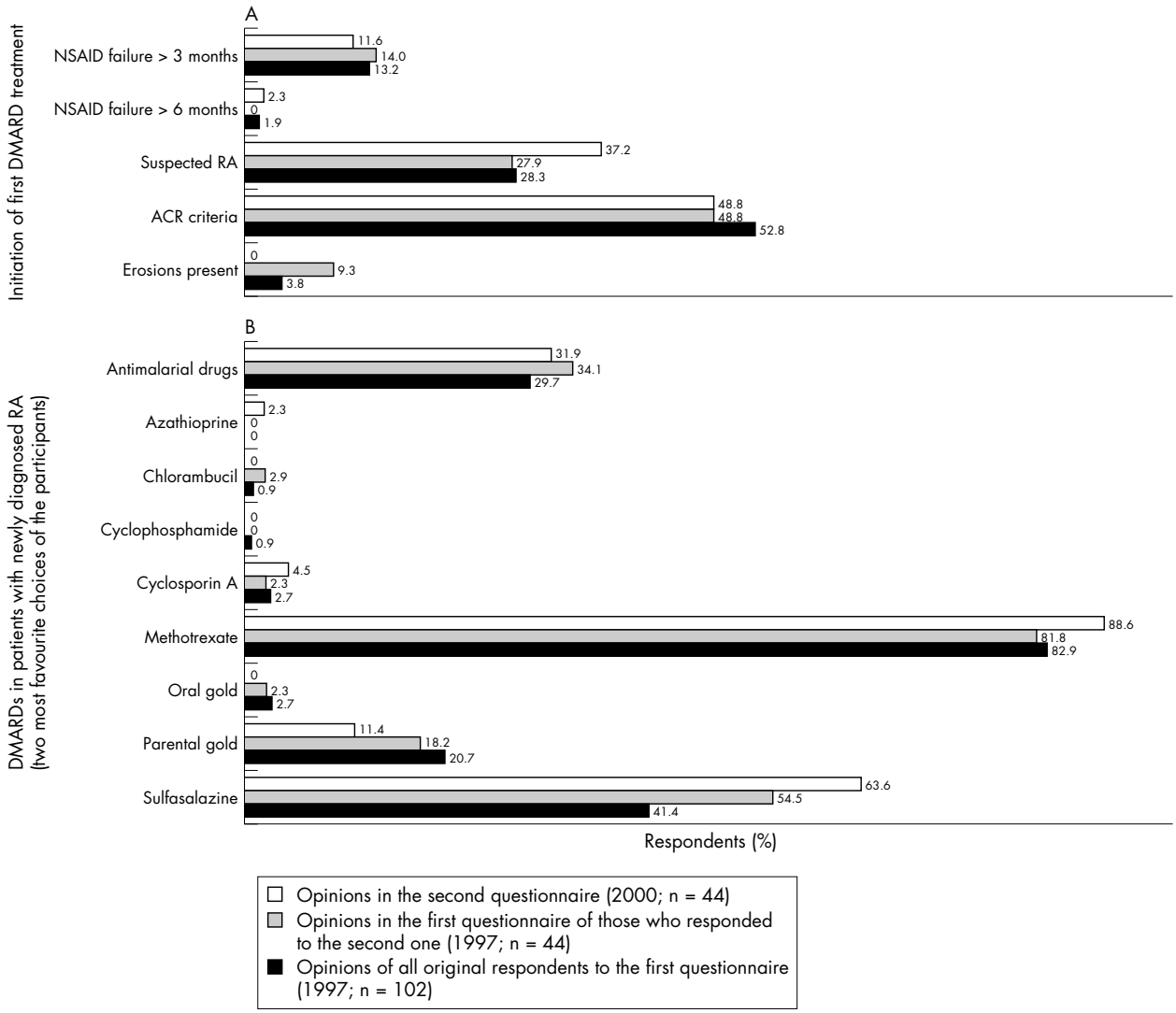


**Figure 2** (A) When do you start DMARD treatment in patients with newly diagnosed RA? (Only one answer was possible): Bars represent the percentage of valid answers. (B) In newly diagnosed patients, which DMARDs do you prescribe most often? (The two most favourite choices were requested): Bars represent the percentage of valid answers.

such recommendations, the importance of recognising early RA and the success of early treatment will be more apparent.

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